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(54) Title: SALT OF A BISPHOSPHONIC ACID DERIVATIVE

(57) Abstract

The present invention relates to an anhydrous dipotassium alendronic acid salt and the dipotassium alendronic acid salt hydrates e.g. dipotassium alendronic acid salt pentahydrate. The present invention also relates to pharmaceutical preparations comprising as active ingredient the anhydrous dipotassium alendronic acid salt one of the dipotassium alendronic acid salt hydrates. The pharmaceutical preparation may be a tablet, a pellet, a film, sugar or enterocoated tablet or pellet, a capsule, a suspension, a solution, an emulsion, etc.

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# SALT OF A BISPHOSPHONIC ACID DERIVATIVE

The present invention relates to the anhydrous dipotassium alendronic acid salt and to the dipotassium alendronic acid salt hydrates. (Alendronic acid stands for 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid.)

Alendronic acid and some of its pharmaceutically acceptable salts are known compounds. Said compounds serve for the treatment of diseases of abnormal (ectopic) depositions of calcium salts and the reduction of bone resorption. As such diseases there may be mentioned, inter alia, osteoporosis, menopausal osteoporosis, Paget's disease, myosisitis ossificans, Bechterew's disease, malignant hypercalcemia, metastatic bone disease, periodontal disease, cholelithiasis, nephrolithiasis, urolithiasis, urinary calculus, sclerosis, arthritis, bursistis, neuritis and tetany.

From WO 96/39410 Specification there are known certain pharmaceutical formulations comprising disodium salts of alendronic acid as well as some new disodium salts. However, it has been found that said salts are not entirely satisfactory, as they irritate the digestion system, in particular the Esophagus and are not very soluble.

It has now surprisingly been found that the anhydrous dipotassium alendronic acid salt and the dipotassium alendronic acid salt hydrates, which so far had not been known, irritate the Esophagus less and are more soluble.

The present invention thus consists in the anhydrous dipotassium alendronic acid salt and in the dipotassium alendronic acid salt hydrates.

The present invention consists also in pharmaceutical preparations comprising as active ingredient the anhydrous dipotassium alendronic acid salt one of the dipotassium alendronic acid salt hydrates.

The pharmaceutical preparation may be a tablet,a pellet, a film, sugar or enterocoated tablet or pellet, a capsule, a suspension, a solution, an emulsion, etc. It may comprise in addition to the active ingredient suitable one or more compounds

selected among suitable carriers, diluents, fillers, solvents, lubricants, disintegrants, preservatives, emulsifiers, etc.

The compounds according to the present invention may be prepared by a reaction of the alendronic acid with potassium hydroxide under suitable reaction conditions.

The present invention will now be illustrated with reference to the Examples without being restricted by them.

Example 1

0.5 N of aqueous potassium hydroxide was added with stirring to an aqueous suspension of 3.97 g of Alendronic Acid in 150 ml of distilled water until the pH was 9.2.

The solution obtained was triturated with 400 ml of ethanol. The suspension obtained was left to stand overnight at 4°C. The precipitated solid was filtered off and dried for 20 hours over $P_2O_5$ in vacuo at 100°C at 26 tor. 3.51 g (yield = 88.4%) of the anhydrous dipotassium alendronic acid salt were obtained.

The compound has the molecular formula: $C_4H_{11}O_7NP_2K_2$

The C H N analysis:

Calc.: H 3.41% C 14.77% N 4.13%

Found: H 3.47% C 14.84% N 4.03%.

Example 2

2 g of the anhydrous dipotassium alendronic acid salt obtained as described in Example 1 were left open on a small glass dish for 24 hours at ambient room conditions. After said period the weight of the product was 2.624 g, i.e.the product gained 0.624 g (31.2%). Thereafter the product was kept under the same conditions for 96 hours. The weight of the product was 2,615 g, 2.635 g and
2.608 g after 48, 72 and 96 hours, respectively. This confirmed that the dipotassium alendronic acid salt pentahydrate was obtained.

The Differential Scanning Calorimetry (DSC) as shown in the annexed Figure and the Thermogravimetric Analysis (TG) confirmed also that said pentahydrate was obtained.

The compound has the molecular formula $C_4H_{11}O_7NP_2K_2.5H_2O$

The H C N analysis:

| | | | |
|---|---|---|---|
| Calc.: | H 5.10% | C 11.57% | N 3.37% |
| Found: | H 5.21% | C 11.33% | N 3.28% |

Example 3

Preparation of the Granulation Wetting Solution containing Dipotassium Alendronic Acid Salt Pentahydrate

144 g of Dipotassium Alendronic Acid Salt Pentahydrate were dissolved in 550 ml of water.

Preparation of the Powder Mixture

550 g of Calcium Hydrogen Phosphate Dihydrate, 400 g of Corn Starch, 900 g of Microcrystalline Cellulose, 135 g of Pregelatinized Starch and 15 g of Crospovidone were passed through a 30 mesh screen and mixed in a fluid bed granulator.

Granulation step

The granulation wetting solution was sprayed on the powder mixture in a fluid bed granulator to obtain a granulate which was then dried in the fluid bed granulator at an inlet temperature of 50°C.

Preparation of Granulate for Encapsulation

The dried granulate was passed through a 16 mesh sieve and mixed in a drum mixer with 4 g of Magnesium Stearate.

Preparation of Tablets

The granulate was compressed into tablets, each tablet containing 16,8 mg of Dipotassium Alendronic Acid Salt Pentahydrate equivalent to 10 mg of Alendronic Acid.

Example 4

Preparation of the Granulation Wetting Solution containing Dipotassium Alendronic Acid Salt Pentahydrate

144 g of Dipotassium Alendronic Acid Salt Pentahydrate were dissolved in 650 ml of water.

Preparation of the Powder Mixture

600 g of Lactose, 300 g of Corn Starch, 950 g of Microcrystalline Cellulose, 135 g of Pregelatinized Starch and 20 g of Croscarmellose Sodium were passed through a 30 mesh screen and mixed in a fluid bed granulator.

Granulation step

The granulation wetting solution was sprayed on the powder mixture in a fluid bed granulator to obtain a granulate which was then dried in the fluid bed granulator at an inlet temperature of 50°C.

Preparation of Granulate for Encapsulation

The dried granulate was passed through a 16 mesh sieve and mixed in a drum mixer with 4 g of Magnesium Stearate.

Preparation of Tablets

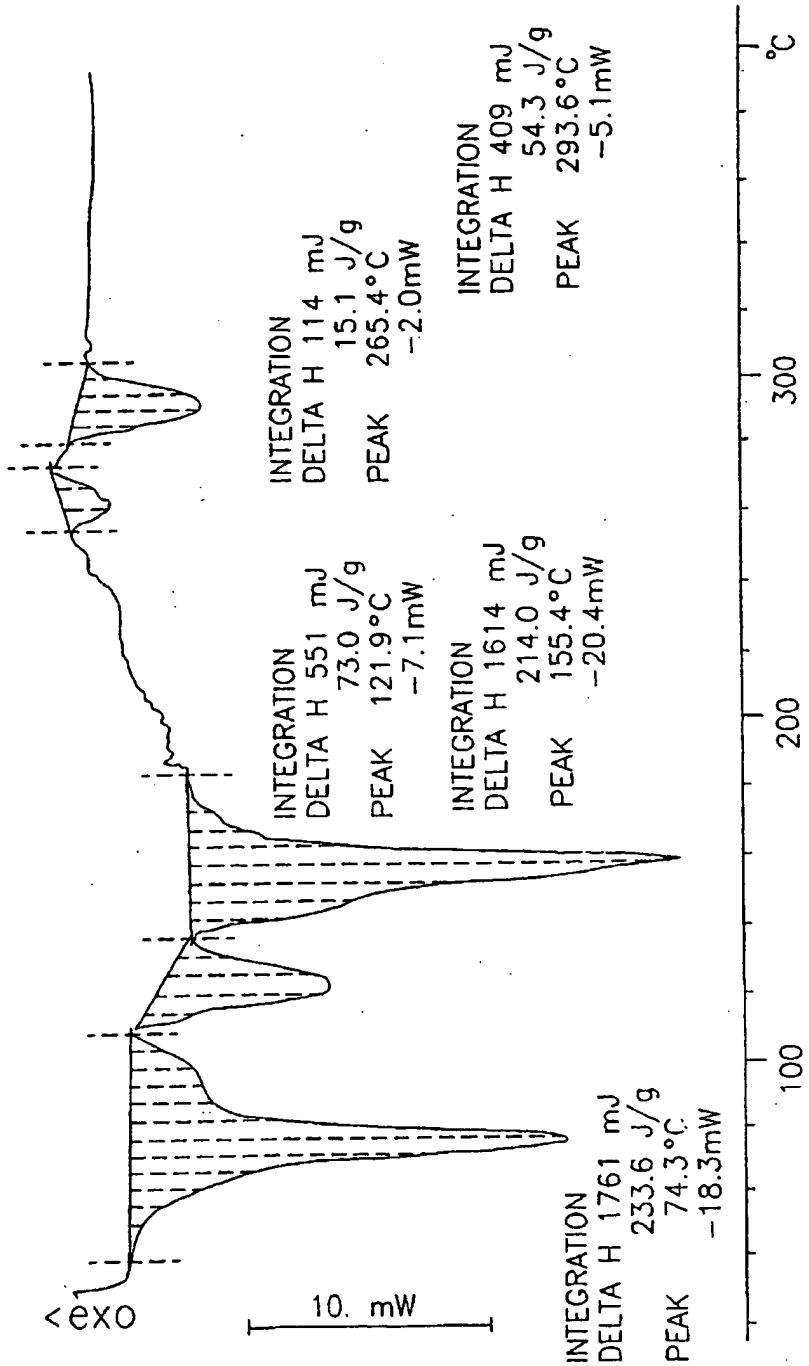
The granulate was compressed into tablets, each tablet containing 16,8 mg of Dipotassium Alendronic Acid Salt Pentahydrate equivalent to 10 mg of Alendronic Acid.

Example 5

144 g of Dipotassuim Alendronic acid salt pentohydrate were mixed with 950 g lactose and 850 g of microcrystalline cellulose.
30 g of Crosspovidone were added to the above blended powders and mixed.
Finally 10 g of Magnesium Stearate were added to the mixed powdres and mixed to an homogenous mixed powders.
The lubricated mixture was compressed to provide tablets, each containing the equivalent of 10 mg Alendronic acid.

Claims

1. The anhydrous dipotassium alendronic acid salt and the dipotassium alendronic acid salt hydrates.
2. The anhydrous dipotassium alendronic acid salt.
3. Dipotassium alendronic acid salt pentahydrate.
4. A pharmaceutical preparation comprising as active ingredient the anhydrous dipotassium alendronic acid salt.
5. A pharmaceutical preparation comprising as active ingredient a dipotassium alendronic acid salt hydrate.
6. A pharmaceutical preparation according to Claim 5, wherein the hydrate is the pentahydrate.
7. A pharmaceutical preparation according to any of Claims 4 to 6 being in the form of a tablet, a pellet, a film , sugar or enterocoated tablet or pellet, a capsule, a solution or an emulsion.
8. A pharmaceutical preparation according to any of Claims 4 to 7 comprising in addition to the active ingredient one or more compounds selected among carriers, diluents, fillers and solvents.
9. A pharmaceutical preparation according to Claim 8 which comprises one or more additives selected among lubricants, disintegrants, preservatives, and emulsifiers.
10. The anhydrous dipotassium alendronic acid salt and the dipotassium alendronic acid salt hydrates as defined in Claim 1 with reference to Examples 1 and 2.


INTEGRATION
DELTA H 1761 mJ
233.6 J/g
PEAK 74.3°C
-18.3mW
INTEGRATION
DELTA H 1614 mJ
214.0 J/g
PEAK 155.4°C
-20.4mW
INTEGRATION
DELTA H 551 mJ
73.0 J/g
PEAK 121.9°C
-7.1mW
INTEGRATION
DELTA H 114 mJ
15.1 J/g
PEAK 265.4°C
-2.0mW
INTEGRATION
DELTA H 409 mJ
54.3 J/g
PEAK 293.6°C
-5.1mW
<exo
10. mW
100
200
300
°C

FIGURE

# INTERNATIONAL SEARCH REPORT

Inte. onal Application No
PCT/IL 98/00508

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07F9/38 A61K31/66

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07F A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

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